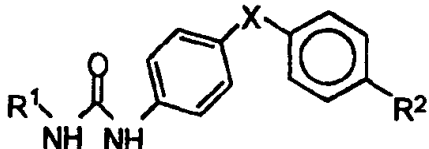




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<p>(21) International Application Number: PCT/SK98/00019</p> <p>(22) International Filing Date: 16 December 1998 (16.12.98)</p> <p>(30) Priority Data: PV 1751-97 19 December 1997 (19.12.97) SK</p> <p>(71) Applicant (for all designated States except US): SLOVAKO-FARMA, A.S. [SK/SK]; Železničná 12, 920 27 Hlohovec (SK).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): OREMUS, Vladimír [SK/SK]; Vysoká 4, 811 06 Bratislava (SK). ŠMAHOVSKÝ, Vendelín [SK/SK]; Novomeského 18, 902 01 Pezinok (SK). FÁBEROVÁ, Viera [SK/SK]; Račianska 12, 831 04 Bratislava (SK). KAKALÍK, Ivan [SK/SK]; 900 81 Šenkvice (SK). SCHMIDTOVÁ, Ľudmila [SK/SK]; Komenského 10, 900 01 Modra (SK). ZEMÁNEK, Marián [SK/SK]; Zochova 16, 811 03 Bratislava (SK).</p> <p>(74) Agent: NEUSCHL, Jozef; Rott, Ružička and Guttmann, Patentová, známková a právna kancelária, v.o.s., Pionierska 15, 831 02 Bratislava (SK).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. With amended claims.</p>
<p>(54) Title: 1,3-DISUBSTITUTED UREAS AS ACAT INHIBITORS, AND METHOD OF PREPARING THEREOF</p> <p>(57) Abstract</p> <p>The invention relates to 1,3-disubstituted ureas of general formula (I) where R¹ is an aryl, R² is nitro and/or amino, and X is oxygen and/or sulfur, and the method of preparing thereof which consists in treating aromatic amines with isocyanates. Isocyanates may be formed in situ and the reaction carried out in toluene, at 80 °C. If the nitro group is formed, it is reduced with hydrogen in the presence of palladium catalyst to the amino group. The obtained 1,3-disubstituted ureas are inhibitors of the activity of the acyl co-enzyme A: cholesterol acyltransferase (ACAT) enzyme, and may be used to inhibit cholesterol esterification and absorption in hypercholesterolemia.</p> <div style="text-align: center;">  <p style="text-align: right;">(1)</p> </div>		

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1,3-Disubstituted Ureas as ACAT Inhibitors, and Method of Preparing Thereof**Technical Field**

The invention relates to compounds the principal characteristics of which include inhibition of the acyl-coenzyme A: cholesterol acyltransferase (ACAT) enzyme activity, and to a method for the preparation of such compounds.

Background Art

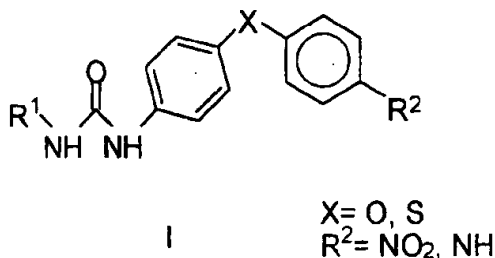
The acyl-coenzyme A: cholesterol O-acyltransferase (EC 2.3.1.26) (ACAT) enzyme is responsible for the catalysis of the intracellular esterification of cholesterol. ACAT is present in most tissues such as the intestine, liver, and arterial wall. The enzyme is assumed to be involved in numerous processes which underlie the development of atherosclerosis, absorption of dietary cholesterol, accumulation of cholesterol esters, hepatic secretion of cholesterol esters into the blood plasma in the form of VLDL cholesterol.

A number of substances of the urea type have been described to inhibit ACAT. We shall show several more recent examples describing 1,3-disubstituted ureas as ACAT enzyme inhibitors. Patents EP 506532, FR 2674522, JP 93097802, US 5219859 describe ureas containing indole derivatives in their molecules. A combination of aromatic and aliphatic moieties has been described in Patents EP 665216, JP 95258199. Introduction into the molecule of a 1,3-dioxolane ring has been reported in Bioorg. Med. Chem. Lett. 1995, 5(15): 1581.

1,3-Disubstituted ureas of the present invention have not been described in literature.

Disclosure of Invention

1,3-Disubstituted ureas of general formula I,



wherein R¹ is 4-nitrophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R² is nitro, and X = O, S; and for R¹ being 2,4-difluorophenyl, 2,3-dichlorophenyl, 2,6-dimethylphenyl, 2,6-di(methylethyl)-phenyl R² is amino, and X = O, S.

The method for the preparation of the above compounds according to this invention consists in reacting an isocyanate (as prepared in situ or as commercially available) with amine to give an urea the nitro group of which may subsequently be reduced to the amino group. Ureas prepared in this way show inhibitory effect on acyl-coenzyme A: cholesterol acyltransferase (ACAT).

Examples**Example 1**

1-(4-Nitrophenyl)-3-((-4'-nitrophenoxy)-phenyl)-urea

A solution of 4-nitrophenylisocyanate in diethylether (20 ml) is added dropwis to a solution of 4'-nitrophenoxy-aniline (2.30 g, 0.01 mol) in a mixture of diethylether (20 ml) and tetrahydrofurane (20 ml) at laboratory temperature, and the mixture is stirred for 16 hours. The precipitated product is aspirated, washed with diethylether (20 ml). The raw product is purified by chromatography on silica gel eluting with dichloromethane-methanol.

¹H-NMR (CDCl₃): 7.11(d, 2H, H-arom.); 7.17(d, 2H, H-arom.); 7.59(d, 2H, H-arom.); 7.70(d, 2H, H-arom.); 8.20(d, 2H, H-arom.); 7.25(d, 2H, H-arom.); 9.05(s, 1H, NH.); 9.46(s, 1H, NH).

¹³C-NMR (CDCl₃): 116.80(CH-arom.); 117.46(CH-arom.); 120.46(CH-arom.); 121.13(CH-arom.); 125.07(CH-arom.); 126.11(CH-arom.); 136.50, 141.00, 141.96, 146.26, 148.86, 151.95(C-arom.); 163.39(C=O).

Analysis for C₁₉H₁₄N₄O₆

%C(calcd/found)	%H	%N
57.85/57.73	3.58/3.61	14.21/14.12

Yield: 92% Melting temp.: 231-234°C

Example 2

1-(2-Fluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2-fluorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for C₁₉H₁₄FN₃O₄

%C(calcd/found)	%H	%N
62.11/62.09	3.84/3.88	11.44/11.29

Yield: 48% Melting temp.: 253-255°C

Example 3

1-(4-Fluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-fluorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{14}FN_3O_4$

%C(calcd/found)	%H	%N
62.11/61.99	3.84/3.85	11.44/11.34

Yield: 59% Melting temp.: 267-269°C

Example 4

1-(2,4-Difluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,4-difluorophenylisocyanate by an analogous procedure to that described in Example 1.

$^1\text{H-NMR}$ (CDCl_3): 6.98-7.18(m, 5H, H-arom.); 7.23-7.37(m, 1H, H-arom.); 7.56(d, 2H, H-arom.); 8.03-8.16(m, 1H, H-arom.); 8.24(d, 2H, H-arom.); 8.50(s, 1H, NH); 9.13(s, 1H, NH).

$^{13}\text{C-NMR}$ (CDCl_3): 103.72(CH-arom.); 110.96(CH-arom.); 116.73(CH-arom.); 119.88(CH-arom.); 121.18(CH-arom.); 122.02(CH-arom.); 126.09(CH-arom.); 136.94, 141.91, 148.48, 152.27, 154.49, 159.80(C-arom.); 163.46(C=O).

Analysis for $C_{19}H_{13}F_2N_3O_4$

%C(calcd/found)	%H	%N
59.22/59.20	3.40/3.53	10.91/10.89

Yield: 85% Melting temp.: 223-224°C

Example 5

1-(2,5-Difluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,5-difluorophenylisocyanate by an analogous procedure to that described in Example 1.

$^1\text{H-NMR}$ (CDCl_3): 6.73-6.88(m, 1H, H-arom.); 7.04-7.35(m, 5H, H-arom.); 7.56(d, 2H, H-arom.); 7.98-8.11(m, 1H, H-arom.); 8.22(d, 2H, H-arom.); 8.75-9.30(br.s., 2H, NH).

$^{13}\text{C-NMR}$ (CDCl_3): 106.56(CH-arom.); 107.75(CH-arom.); 115.67(CH-arom.); 116.74(CH-arom.); 120.03(CH-arom.); 121.21(CH-arom.); 126.08(CH-arom.); 128.82, 136.62, 141.95, 148.73, 151.95, 155.65, 160.38(C-arom.); 163.42(C=O).

Analysis for $C_{19}H_{13}F_2N_3O_4$

%C(calcd/found)	%H	%N
59.22/59.07	3.40/3.49	10.91/10.83

Yield: 76% Melting temp.: 207-208°C

Example 6

1-(2,6-Difluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-difluorophenylisocyanate by an analogous procedure to that described in Example 1.

$^1\text{H-NMR}$ (CDCl_3): 6.95-7.26(m, 6H, H-arom.); 7.42-7.56(m, 2H, H-arom.); 8.01-8.23(m, 3H, H-arom.); 8.94-9.05(m, 2H, NH).

$^{13}\text{C-NMR}$ (CDCl_3): 111.77(CH-arom.); 116.82(CH-arom.); 120.06(CH-arom.); 121.18(CH-arom.); 126.19(CH-arom.); 127.11(CH-arom.); 137.31, 141.99, 148.49, 152.61, 155.65, 160.57(C-arom.); 163.61(C=O).

Analysis for $C_{19}H_{13}F_2N_3O_4$

%C(calcd/found)	%H	%N
59.22/59.10	3.40/3.55	10.91/10.78

Yield: 75% Melting temp.: 231-232°C

Example 7

1-(2-Chlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2-chlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{14}ClN_3O_4$

%C(calcd/found)	%H	%N	%Cl
59.46/59.37	3.68/3.82	10.95/10.78	9.24/8.99

Yield: 63% Melting temp.: 195-197°C

Example 8

1-(4-Chlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-chlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{14}ClN_3O_4$

%C(calcd/found)	%H	%N	%Cl
59.46/59.37	3.68/3.77	10.95/10.84	9.24/9.02

Yield: 69% Melting temp.: 234-236°C

Example 9

1-(2,3-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,3-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.50	3.13/3.31	10.05/9.78	16.95/16.91

Yield: 74% Melting temp.: 199-201°C

Example 10

1-(2,4-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.49	3.13/3.21	10.05/9.80	16.95/16.59

Yield: 71% Melting temp.: 267-269°C

Example 11

1-(2,6-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.39	3.13/3.20	10.05/9.92	16.95/16.81

Yield: 68% Melting temp.: 195-198°C

Example 12

1-(3,4-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 3,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.49	3.13/3.23	10.05/9.89	16.95/16.78

Yield: 80% Melting temp.: 179-180°C

Example 13

1-(3,5-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 3,5-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{19}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.48	3.13/3.30	10.05/10.01	16.95/17.24

Yield: 56% Melting temp.: 213-216°C

Example 14

1-(2-Methylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2-methylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{20}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
60.11/65.96	4.72/4.89	11.56/11.48

Yield: 59% Melting temp.: 112-116°C

Example 15

1-(4-Methylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-methylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{20}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
66.11/66.02	4.72/4.87	11.56/11.40

Yield: 64% Melting temp.: 168-170°C

Example 16

1-(2,4-Dimethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,4-dimethylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{21}H_{19}N_3O_4$

%C(calcd/found)	%H	%N
66.83/66.87	5.07/5.10	11.13/11.05

Yield: 73% Melting temp.: 165-169°C

Example 17

1-(2,6-Dimethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-dimethylphenylisocyanate by an analogous procedure to that described in Example 1.

$^1\text{H-NMR}$ (CDCl_3): 2.22(s, 6H, CH_3); 7.04-7.17(m, 7H, H-arom.); 7.57(m, 2H, H-arom.); 7.74(s, 1H, NH); 8.23(d, 2H, H-arom.); 8.87(s, 1H, NH).

$^{13}\text{C-NMR}$ (CDCl_3): 18.19(2x CH_3); 116.61(CH-arom.); 119.54(CH-arom.); 121.08(CH-arom.); 126.07(CH-arom.); 127.67(CH-arom.); 135.53(CH-arom.); 125.93, 135.51, 137.95, 141.82, 147.87, 153.10(CH-arom.); 163.64(C=O).

Analysis for $C_{21}H_{19}N_3O_4$

%C(calcd/found)	%H	%N
66.83/66.67	5.07/5.18	11.13/10.98

Yield: 68% Melting temp.: 249-250°C

Example 18

1-(3,5-Dimethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 3,5-dimethylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{21}H_{19}N_3O_4$

%C(calcd/found)	%H	%N
66.83/66.78	5.07/5.22	11.13/11.06

Yield: 58% Melting temp.: 145-147°C

Example 19

1-(2,6-Di-(methylethyl)-phenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-di-(methylethyl)phenylisocyanate by an analogous procedure to that described in Example 1.

¹H-NMR (CDCl₃): 1.18(d, 6H, 2xCH₃); 3.22(hept., 2H, 2xCH); 7.06-7.30(m, 7H, H-arom.); 7.56(d, 2H, H-arom.); 7.63(s, 1H, NH); 8.23(d, 2H, H-arom.); 8.78(s, 1H, NH).

¹³C-NMR (CDCl₃): 23.31(2xCH₃); 27.86(2xCH); 116.58(CH-arom.); 119.44(CH-arom.); 120.86(CH-arom.); 122.72(CH-arom.); 125.87(CH-arom.); 146.53(CH-arom.); 127.08, 132.14, 137.80, 141.83, 147.89, 154.10(C-arom.); 163.46(C=O).

Analysis for C₂₆H₂₇N₃O₄

%C(calcd/found)	%H	%N
69.27/69.13	6.28/6.34	9.69/9.56

Yield: 88% Melting temp.: 208-210°C

Example 20

1-(2-Trifluoromethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

4'-Nitrophenoxy-aniline (1.0 g, 4.3 mmol), triphosgene (0.43 g, 1.44 mmol), triethylamine (0.6 ml, 4.3 mmol) are heated in toluene (15 ml) in a pressure tube at 80°C for 20 hours. Then, 2-trifluoromethylaniline (0.53 ml, 4.3 mmol) and triethylamine (0.6 ml, 4.3 mmol) in toluene (10 ml) are added. The mixture is heated at 80°C for 4 hours, then it is concentrated, and the product is isolated using chromatography on silica gel eluting with dichloromethane - methanol.

Analysis for C₂₀H₁₄F₃N₃O₄

%C(calcd/found)	%H	%N
57.56/57.60	3.38/3.44	10.07/9.89

Yield: 67% Melting temp.: 201-203°C

Example 21

1-(3-Trifluoromethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 3-trifluoromethylaniline by an analogous procedure to that described in Example 20.

Analysis for $C_{20}H_{14}F_3N_3O_4$

%C(calcd/found)	%H	%N
57.56/57.66	3.38/3.45	10.07/9.96

Yield: 72% Melting temp.: 208-211°C

Example 22

1-(4-Trifluoromethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-trifluoromethylaniline by an analogous procedure to that described in Example 20.

Analysis for $C_{20}H_{14}F_3N_3O_4$

%C(calcd/found)	%H	%N
57.56/57.48	3.38/3.41	10.07/10.00

Yield: 45% Melting temp.: 185-189°C

Example 23

1-(2-Pyridyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2-pyridylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{18}H_{14}N_4O_4$

%C(calcd/found)	%H	%N
61.71/61.67	4.03/4.06	15.99/15.79

Yield: 76% Melting temp.: 143-146°C

Example 24

1-(3-Pyridyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 3-pyridylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{18}H_{14}N_4O_4$

%C(calcd/found)	%H	%N
61.71/61.58	4.03/4.21	15.99/15.87

Yield: 69% Melting temp.: 177-179°C

Example 25

1-(4-Pyridyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-pyridylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{18}H_{14}N_4O_4$

%C(calcd/found)	%H	%N
61.71/61.66	4.03/4.11	15.99/15.87

Yield: 72% Melting temp.: 126-127°C

Example 26

1-(1-Naphthyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 1-naphthylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{23}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
69.17/69.23	4.29/4.41	10.52/10.46

Yield: 82% Melting temp.: 117-119°C

Example 27

1-(2-Naphthyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 1-naphthylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{23}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
69.17/69.09	4.29/4.36	10.52/10.38

Yield: 69% Melting temp.: 103-106°C

Example 28

1-(1-Adamantyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 1-adamantylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{23}H_{25}N_3O_4$

%C(calcd/found)	%H	%N
67.80/67.65	6.18/6.23	10.31/10.16

Yield: 61% Melting temp.: 143-146°C

Example 29

1-(4-Nitrophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

A solution of 4-nitrophenylisocyanate in diethylether (20 ml) is added dropwise to a solution of 4'-nitrophenylthio-aniline (2.46 g, 0.01 mol) in a mixture of diethylether (20 ml) and tetrahydrofurane (20 ml) at laboratory temperature, and the mixture is stirred for 16 hours. The resulting product is aspirated, washed with diethylether (20 ml). The crude product is purified by chromatography on silica gel eluting with dichloromethane and methanol.

Analysis for $C_{18}H_{14}N_4O_5S$

%C(calcd/found)	%H	%N	S%
55.61/55.52	3.44/3.49	13.65/13.59	7.81/7.67

Yield: 56% Melting temp.: 164-167°C

Example 30

1-(2-Fluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-fluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{18}H_{14}FN_3O_3S$

%C(calcd/found)	%H	%N	S%
59.52/59.41	3.68/3.77	10.96/11.04	8.36/8.41

Yield: 61% Melting temp.: 274-277°C

Example 31

1-(4-Fluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-fluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{14}FN_3O_3S$

%C(calcd/found)	%H	%N	S%
59.52/59.46	3.68/3.71	10.96/10.87	8.36/8.18

Yield: 59% Melting temp.: 287-290°C

Example 32

1-(2,4-Difluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,4-difluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}F_2N_3O_3S$

%C(calcd/found)	%H	%N	S%
56.86/56.78	3.26/3.39	10.47/10.41	7.99/7.86

Yield: 57% Melting temp.: 268-271°C

Example 33

1-(2,5-Difluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,5-difluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}F_2N_3O_3S$

%C(calcd/found)	%H	%N	S%
56.86/56.76	3.26/3.37	10.47/10.35	7.99/8.05

Yield: 64% Melting temp.: 259-261°C

Example 34

1-(2,6-Difluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,6-difluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}F_2N_3O_3S$

%C(calcd/found)	%H	%N	S%
56.86/56.69	3.26/3.34	10.47/10.43	7.99/7.81

Yield: 68% Melting temp.: 263-265°C

Example 35

1-(2-Chlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-chlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{14}ClN_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
57.07/57.01	3.53/3.62	10.51/11.46	8.87/8.65	8.02/7.95

Yield: 65% Melting temp.: 231-233°C

Example 36

1-(4-Chlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-chlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{14}ClN_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
57.07/56.97	3.53/3.57	10.51/10.45	8.87/8.81	8.02/7.86

Yield: 63% Melting temp.: 206-209°C

Example 37

1-(2,3-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,3-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.46	3.02/3.07	9.68/9.62	16.33/16.27	7.38/7.50

Yield: 75% Melting temp.: 157-159°C

Example 38

1-(2,4-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-uracil

The title compound was prepared from 2,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.57	3.02/3.21	9.68/9.54	16.33/16.35	7.38/7.28

Yield: 57% Melting temp.: 174-178°C

Example 39

1-(2,6-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,6-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.51	3.02/3.07	9.68/9.73	16.33/16.25	7.38/7.19

Yield: 83% Melting temp.: 164-167°C

Example 40

1-(3,4-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 3,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.47	3.02/3.14	9.68/9.57	16.33/16.09	7.38/7.24

Yield: 57% Melting temp.: 238-240°C

Example 41

1-(3,5-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 3,5-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.47	3.02/3.11	9.68/9.59	16.33/16.21	7.38/7.41

Yield: 67% Melting temp.: 185 - 188°C

Example 42

1-(2-Methylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-methylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{20}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
63.31/63.22	4.52/4.66	11.07/10.79	8.45/8.34

Yield: 78% Melting temp.: 229-234°C

Example 43

1-(4-Methylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-methylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{20}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
63.31/63.25	4.52/4.63	11.07/11.12	8.45/8.35

Yield: 73% Melting temp.: 163-166°C

Example 44

1-(2,4-Dimethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,4-dimethylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{21}H_{19}N_3O_3S$

%C(calcd/found)	%H	%N	S%
64.11/64.08	4.87/4.83	10.68/10.59	8.15/7.95

Yield: 65% Melting temp.: 209-213°C

Example 45

1-(2,6-Dimethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,6-dimethylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{21}H_{19}N_3O_3S$

%C(calcd/found)	%H	%N	S%
64.11/63.97	4.87/4.83	10.68/10.47	8.15/8.01

Yield: 72% Melting temp.: 264-267°C

Example 46

1-(3,5-Dimethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 3,5-dimethylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{21}H_{19}N_3O_3S$

%C(calcd/found)	%H	%N	S%
64.11/64.04	4.87/4.99	10.68/10.63	8.15/8.01

Yield: 68% Melting temp.: 194-196°C

Example 47

1-(2,6-Dimethylethyl)-phenyl-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,6-(methylethyl)-phenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{26}H_{27}N_3O_3S$

%C(calcd/found)	%H	%N	S%
66.79/66.72	6.06/6.17	9.35/9.27	7.12/6.96

Yield: 72% Melting temp.: 175-177°C

Example 48

1-(2-Trifluoromethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

4'-Nitrophenylthio-aniline (1.06 g, 4.3 mmol), triphosgene (0.43 g, 1.44 mmol), triethylamine (0.6 g, 4.3 mmol) in toluene (15 ml) are heated in a pressure tube at 80°C for 20 hours. Subsequently, 2-trifluoromethylaniline (0.53 ml, 4.3 mmol)

and triethylamine (0.6 ml, 4.3 mmol) in toluene (10 ml) are added. The mixture is heated at 80°C for 4 hours, then concentrated, and the product is separated by chromatography on silica gel eluting with dichloromethane-methanol.

Analysis for $C_{20}H_{14}F_3N_3O_3S$

%C(calcd/found)	%H	%N	S%
55.43/55.38	3.26/3.39	9.70/9.71	7.40/7.35

Yield: 52% Melting temp.: 257-261°C

Example 49

1-(3-Trifluoromethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 3-trifluorophenylisocyanate by an analogous procedure to that described in Example 48.

Analysis for $C_{20}H_{14}F_3N_3O_3S$

%C(calcd/found)	%H	%N	S%
55.43/55.21	3.26/3.38	9.70/9.53	7.40/7.31

Yield: 65% Melting temp.: 241-244°C

Example 50

1-(4-Trifluoromethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-trifluorophenylisocyanate by an analogous procedure to that described in Example 48.

Analysis for $C_{20}H_{14}F_3N_3O_3S$

%C(calcd/found)	%H	%N	S%
55.43/55.37	3.26/3.33	9.70/9.81	7.40/7.28

Yield: 51% Melting temp.: 254-257°C

Example 51

1-(2-Pyridyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-pyridylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{18}H_{14}N_4O_3S$

%C(calcd/found)	%H	%N	S%
59.01/58.86	3.85/3.91	15.29/15.23	8.75/8.80

Yield: 48% Melting temp.: 278-281°C

Example 52

1-(3-Pyridyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 3-pyridylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{18}H_{14}N_4O_3S$

%C(calcd/found)	%H	%N	S%
59.01/58.99	3.85/3.99	15.29/15.25	8.75/8.49

Yield: 63% Melting temp.: 261-264°C

Example 53

1-(4-Pyridyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-pyridylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{18}H_{14}N_4O_3S$

%C(calcd/found)	%H	%N	S%
59.01/58.92	3.85/3.76	15.29/15.32	8.75/8.67

Yield: 69% Melting temp.: 190-192°C

Example 54

1-(1-Naphthyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 1-naphthylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{23}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
66.49/66.53	4.13/4.21	10.12/10.17	7.70/7.54

Yield: 56% Melting temp.: 164-168°C

Example 55

1-(2-Naphthyl)-3-((4'-nitrophenylthio)-phenyl)-ur a

The title compound was prepar d from 2-naphthylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{23}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
66.49/66.47	4.13/4.25	10.12/10.06	7.70/7.57

Yield: 69% Melting temp.: 142-147°C

Example 56

1-(1-Adamantyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 1-adamantylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{23}H_{25}N_3O_3S$

%C(calcd/found)	%H	%N	S%
65.22/65.17	5.95/6.03	9.93/10.02	7.56/7.38

Yield: 52% Melting temp.: 264-267°C

Example 57

1-(2,4-Difluorophenyl)-3-((4'-aminophenoxy)-phenyl)-urea

One gram of compound 4 is dissolved in methanol (20 ml) and 0.1 g of 10% palladium on charcoal is added. The mixture is stirred under hydrogen atmosphere (at atmospheric pressure) for 20 hours. Subsequently, 100 ml methanol is added and the catalyst is removed by filtering. The product is then obtained by concentrating the methanolic solution.

Analysis for $C_{19}H_{15}F_2N_3O_2$

%C(calcd/found)	%H	%N
64.22/64.09	4.25/4.29	11.83/12.01

Yield: 88% Melting temp.: 248-251°C

Example 58

1-(2,5-Dichlorophenyl)-3-((4'-aminophenoxy)-phenyl)-urea

The title compound was prepared from compound 9 by an analogous procedure to that described in Example 57.

Analysis for $C_{19}H_{15}Cl_2N_3O_2$

%C(calcd/found)	%H	%N	%Cl
58.78/58.45	3.89/3.94	10.82/10.78	18.26/18.11

Yield: 91% Melting temp.: 201-204°C

Example 59

1-(2,6-Dimethylphenyl)-3-((4'-aminophenoxy)-phenyl)-urea

The title compound was prepared from compound 17 by an analogous procedure to that described in Example 57.

Analysis for $C_{21}H_{21}N_3O_2$

%C(calcd/found)	%H	%N
72.60/72.45	6.09/6.13	12.10/12.02

Yield: 85% Melting temp.: 225-227°C

Example 60

1-(2,6-Di(methylethyl)-phenyl)-3-((4'-aminophenoxy)-phenyl)-urea

The title compound was prepared from compound 19 by an analogous procedure to that described in Example 57.

1H -NMR ($CDCl_3$): 1.15(d, 6H, 2xCH₃); 3.15(hept., 2H, 2xCH); 4.86(s, 2H, NH); 6.57(d, 2H, H-arom.); 6.72(d, 2H, H-arom.); 6.81(d, 2H, H-arom.); 7.10-1.28(m, 3H, H-arom.); 7.36(d, 2H, H-arom.); 7.56(s, 1H, HN); 8.58(br.s., 1H, NH).

^{13}C -NMR ($CDCl_3$): 23.43(2xCH₃); 27.93(2xCH); 114.63(CH-arom.); 117.55(CH-arom.); 119.09(CH-arom.); 199.43(CH-arom.); 122.79(CH-arom.); 127.11(CH-arom.); 127.11(CH-arom.); 132.40, 134.86, 144.77, 146.61, 146.89, 152.88(C-arom.); 154.36(C=O).

Analysis for $C_{25}H_{29}N_3O_2$

%C(calcd/found)	%H	%N
74.41/74.54	7.24/7.33	10.41/10.34

Yield: 90% Melting temp.: 219-221°C

Example 61

1-(2,4-Difluorophenyl)-3-((4'-aminophenylthio)-phenyl)-urea

The title compound was prepared from compound 32 by an analogous procedure to that described in Example 57.

Analysis for $C_{19}H_{15}F_2N_3OS$

%C(calcd/found)	%H	%N	%S
61.44/61.56	4.07/4.18	11.31/11.15	8.63/8.51

Yield: 79% Melting temp.: exceeding 300°C

Example 62

1-(2,3-Dichlorophenyl)-3-((4'-aminophenylthio)-phenyl)-urea

The title compound was prepared from compound 37 by an analogous procedure to that described in Example 57.

Analysis for $C_{19}H_{15}Cl_2N_3OS$

%C(calcd/found)	%H	%N	%Cl	%S
56.44/56.35	3.74/3.80	10.39/10.41	17.54/17.57	7.93/7.59

Yield: 88% Melting temp.: 259-261°C

Example 63

1-(2,6-Dimethylphenyl)-3-((4'-aminophenylthio)-phenyl)-urea

The title compound was prepared from compound 45 by an analogous procedure to that described in Example 57.

Analysis for $C_{21}H_{21}N_3OS$

%C(calcd/found)	%H	%N	%S
69.39/69.32	5.82/5.93	11.56/11.49	8.28/8.54

Yield: 94% Melting temp.: 198-202°C

Example 64

1-(2,6-Di-(methylethyl)-phenyl)-3-((4'-aminophenylthio)-phenyl)-urea

The title compound was prepared from compound 47 by an analogous procedure to that described in Example 57.

Analysis for $C_{25}H_{29}N_3OS$

%C(calcd/found)	%H	%N	%S
71.56/71.55	6.97/6.89	10.01/10.11	7.64/7.58

Yield: 83% Melting temp.: 267-271 °C

Tests

The biological activity of the substances was evaluated based on the in vitro inhibition of acylCoA:cholesterol acyltransferase (ACAT) activity. The enzyme was obtained from the microsomal fraction of rat liver cells and rabbit intestinal mucosa of animals fed with cholesterol. The substrates for the enzyme reaction included exogenous oleoyl co-enzyme A and endogenous cholesterol. ^{14}C -oleoyl co-enzyme A conversion to ^{14}C -cholesteryl oleate was monitored. From the mixture of extracted lipids, cholesteryl oleate was separated using thin-layer chromatography, and was quantified radiometrically. ACAT specific activity was expressed as the amount of cholesteryl oleate formed per minute per mg microsomal protein.

Table 1 shows percentages of ACAT inhibition in the rat liver and the rabbit intestinal mucosa at various concentrations of the substances tested. Efficiency was calculated as compared to enzyme activity measured in the presence of 1% dimethylsulfoxide used as the solvent to prepare solutions of the substances tested.

Table 1

Inhibitory effect on rat liver and rabbit intestinal mucosa ACAT activity

No	Efficiency	(%)	Concentration	No	Efficiency	(%)	Concentration
	<i>liver</i>	<i>mucosa</i>	(μ M)		<i>liver</i>	<i>mucosa</i>	(μ M)
1	0	46	2	33	0	16	2
2	15	32	2	34	11	25	2
3	0	24	2	35	20	26	2
4	37	55	2	36	12	21	2
5	49	58	2	37	0	0	2
6	0	42	2	38	12	16	2
7	0	0	2	39	15	21	2
8	17	13	2	40	0	20	2
9	58	51	2	41	0	0	2
10	10	26	2	42	27	31	2
11	20	25	2	43	21	32	2
12	11	57	2	44	19	31	2
13	0	0	2	45	23	34	2
14	0	0	2	46	18	27	2
15	0	0	2	47	88	71	2
16	0	0	2	48	25	38	2
17	41	65	2	49	34	45	2
18	0	0	2	50	23	25	2
19	50	67	2	51	48	46	2
20	46	42	2	52	45	36	2
21	38	45	2	53	53	35	2
22	25	18	2	54	24	36	2
23	26	34	2	55	16	31	2
24	0	0	2	56	45	56	2
25	11	17	2	57	53	64	2
26	14	22	2	58	55	46	2

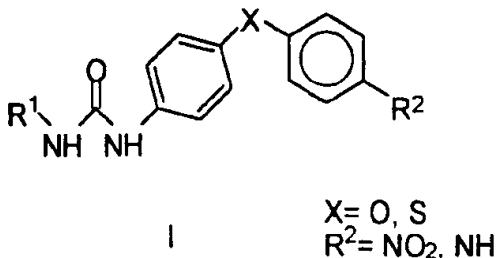
27	0	12	2	59	38	62	2
28	43	58	2	60	68	64	2
29	0	34	2	61	22	25	2
30	0	23	2	62	15	26	2
31	25	27	2	63	21	29	2
32	16	23	2	64	56	67	2

Industrial Applicability

The compounds according to the invention and the method of preparing thereof can be used in pharmaceutical production to make preparations with inhibitory effect on the enzyme acyl co-enzyme A and on cholesterol absorption in hypercholesterolemia.

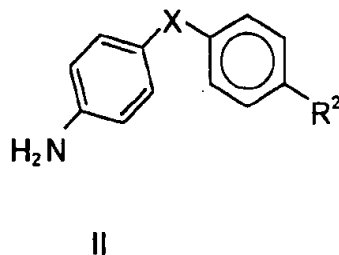
C L A I M S

1. 1,3-Disubstituted ureas of general formula I,



wherein R¹ is 4-nitrophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R² is nitro, and X = O, S; and for R¹ being 2,4-difluorophenyl, 2,3-dichlorophenyl, 2,6-dimethylphenyl, 2,6-di(methylethyl)-phenyl R² is amino, and X = O, S.

2. A method of preparing 1,3-disubstituted ureas of general formula I according to claim 1, characterized in that an amine of general formula II,



wherein R^2 and X have the above defined meanings, is treated with an isocyanate of general formula III,



wherein R^1 has the above defined meaning, said isocyanate optionally being formed in situ from appropriate reactants,

thus giving the above defined urea.

3. The method of claim 2, characterized in that when said isocyanate is formed in situ, the reaction is carried out in toluene at about 80°C.

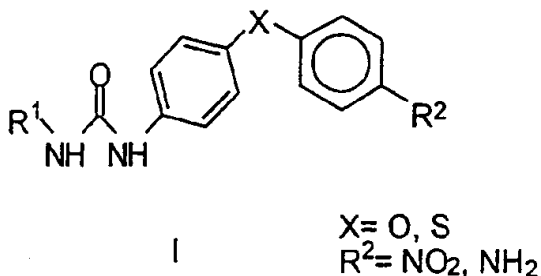
4. The method of any of the preceding claims, characterized in that the obtained 1,3-disubstituted urea of general formula I wherein R^2 means nitro, is treated with hydrogen in the presence of palladium catalyst to reduce the nitro group to the amino group.

5. 1,3-Disubstituted ureas of general formula I, according to claim 1 and/or prepared by the method of claim 2 to 4, characterized in that they have inhibitory effect on the acyl co-enzyme A:cholesterol acyltransferase (ACAT) enzyme.

AMENDED CLAIMS

[received by the International Bureau on 08 June 1999 (08.06.99);
original claim 1 amended remaining claims unchanged (2 pages)]

1. 1,3-Disubstituted ureas of general formula I,

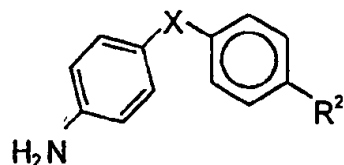


wherein R¹ is 2-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,3-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R² is nitro, and X = O;

wherein R¹ is 4-nitrophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R² is nitro, and X = S;

and for R¹ being 2,4-difluorophenyl, 2,3-dichlorophenyl, 2,6-dimethylphenyl, 2,6-di(methylethyl)-phenyl R² is amino, and X = O, S.

2. A method of preparing 1,3-disubstituted ureas of general formula I according to claim 1, characterized in that an amine of general formula II,



II

wherein R^2 and X have the above defined meanings, is treated with an isocyanate of general formula III,



III

wherein R^1 has the above defined meaning, said isocyanate optionally being formed in situ from appropriate reactants,

thus giving the above defined urea.

3. The method of claim 2, characterized in that when said isocyanate is formed in situ, the reaction is carried out in toluene at about 80°C .

4. The method of any of the preceding claims, characterized in that the obtained 1,3-disubstituted urea of general formula I wherein R^2 means nitro, is treated with hydrogen in the presence of palladium catalyst to reduce the nitro group to the amino group.

5. 1,3-Disubstituted ureas of general formula I, according to claim 1 and/or prepared by the method of claim 2 to 4, characterized in that they have inhibitory effect on the acyl co-enzyme A:cholesterol acyltransferase (ACAT) enzyme.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/SK 98/00019

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C275/36 C07C323/44 C07D213/75 //A61K31/17,A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 284 433 A (H. J. BECKER ET AL) 8 November 1966 see claims 6,8 see examples	1,2
X	EP 0 709 225 A (NIPPON PAPER INDUSTRIES CO) 1 May 1996 see page 15, line 35	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

31 March 1999

Date of mailing of the international search report

12/04/1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

I. International Application No

PCT/SK 98/00019

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